REMARKS

I. Preliminary Remarks

In the Office Action, the Examiner stated that claims 78-99 stand withdrawn from consideration pursuant to 37 C.F.R. § 1.142(b). Applicants have canceled claims 78-99 without prejudice by the foregoing amendment. The currently pending claims are 62, 63, 65-71 and 75-77 as amended and new claims 100-112. The Applicants reserve the right to pursue claims of same or similar subject matter of the canceled claims in continuing applications.

Applicants have also added a sequence listing in compliance with sequence listing requirements. The table below shows how the sequences of the sequence listing correspond to the sequences in the figures and the claimed peptides of p55 and p75 TNF receptor in the specification. Applicants note that SEQ ID NOS: 3 and 4 are identical to Figure 4 except they also include the sequence correction noted at page 35, lines 32-36 of Example 8 (amino acid at position 3 is Thr instead of Ser as it is encoded by "ACC" not "TCC").

SEQ ID NO:	As Reference in the Specification	Page and Line Number
1	p55 kD TNF Receptor cDNA sequence	Figure 1; page 4, lines 16-21
2	p55 kD TNF Receptor deduced amino acid sequence	Figure 1; page 4, lines 16-21
3	p75 kD TNF Receptor cDNA sequence	Figure 4; page 4, lines 35-36
4	p75 kD TNF Receptor deduced amino acid sequence	Figure 4; page 4, lines 35-36
5	Peptide IA	page 7, lines 27-29
8	Peptide IIB	page 7, line 34
10	Peptide IID	page 8, lines 5-6
12	Peptide IIF	page 8, line 8

II. Basis and Support for Amendments

The pending claims are directed to recombinant fusion proteins comprising a soluble fragment of a TNF receptor protein, having a molecular weight of about 55 kD or about 75 kD, fused to all of the domains of the constant region of a human immunoglobulin heavy chain other than the first domain of said constant region.

The amendments to the claims and new claims 100-118 are supported by the specification throughout, e.g. at page 11, lines 1-10, and do not add new matter to the application. Amendments to the claims were also made to render them consistent with the sequences as set forth in the sequence listing. Specific support for the newly added language in the claims is described in the following paragraphs.

Claim 107 is essentially the same as claim 48 which was presented in the original preliminary amendment as filed and was previously examined by the Patent Office, except that it adds reference to SEQ ID NOS: 2 and 4 (displayed in Figures 1 and 4, respectively). Claim 100 and 108 recites a fragment of the p55 TNF receptor that is specifically identified in the specification at page 7, lines 27-29. Claims 102, 103, 106, 110 and 111 recite fragments of the p75 TNF receptor that are specifically identified as the peptides taught in the specification, *e.g.*, at page 7, line 34 (peptide IIB, VFCT), page 8, lines 5-6 (peptide IID, LPAEVAFXPYAPEPGSTC) and page 8, line 8 (peptide IIF, LCAP).

Support for the language in the claims that the claimed proteins specifically bind tumor necrosis factor is found throughout the specification in the concept that the invention is directed to TNF binding proteins, including in Example 1 (page 21, lines 6-22) which notes that the desired TNF binding proteins have specific TNF binding activity.

In claims 105, 106 and 113, the selection of IgG, including IgG1 or IgG3, as the type of heavy chain is supported, e.g., at page 11, lines 1-10.

Claim 114 is directed to compositions comprising pharmaceutically acceptable carrier material. This claim is supported, *e.g.*, at page 12, lines 10-15.

Claims 115 and 117 are directed to methods of making a recombinant protein comprising the steps of culturing a host cell which expresses a polynucleotide encoding a soluble fragment of the invention and isolating the soluble fragment from the host cell or culture supernatant. These claims are supported throughout the specification, e.g., at page 6, lines 22-29 and page 12, lines 4-8.

III. Remarks

The outstanding rejections under 35 U.S.C. §§ 101 and 102 are believed to be mooted by the amendments herein.

Applicants present the following evidence to make available to the Examiner additional data relevant to the presently pending claims:

(1) a "Declaration [II] of Dr. Werner Lesslauer Under 37 § C.F.R. 1.132" (denoted as "Lesslauer Declaration [II]" and attached hereto as **Exhibit A**), which was previously submitted with the amendment mailed February 25, 1997 in the present application;

(2) a "Declaration under 37 C.F.R. § 1.132 of Dr. Werner Lesslauer" (denoted as "Lesslauer Declaration [III]" and attached hereto as **Exhibit B**), previously submitted in an application, U.S. Serial No. 08/444,791, that claims the same priority as the present application; and

(3) Mohler et al., *J. Immunol.* 151:1548-1561, 1993 (denoted as "Mohler *et al.*" and attached hereto as **Exhibit C**).

These exhibits collectively provide evidence with respect to 55 kD TNFR/IgG3 fusion proteins, 75 kD TNFR/IgG3 fusion proteins and 75 kD TNFR/IgG1 fusion proteins.

Lesslauer Declaration [II] provides experimental evidence demonstrating unexpectedly superior activity of a recombinant fusion protein comprising the extracellular domain of the 55 kD TNF receptor (also known as TNFR-I) fused to the hinge region of IgG3 (denoted as "55 TNFR/IgG" in the declaration), compared to the soluble TNFR fragment alone. At page 6, Dr. Lesslauer states that the 55 kD TNFR/IgG fusion protein has at least a 3-fold smaller Kd, and therefore at least three times greater binding affinity, than the corresponding soluble TNFR fragment. On the same page, Dr. Lesslauer states that the IgG3 fusion protein was markedly more effective than the soluble TNFR fragment at neutralizing TNF cytotoxicity *in vitro*. See also the statements at pages 8-9 (paragraphs 1-2) of the declaration. Dr. Lesslauer compares these results to activity of a CD4/IgG fusion which was reported to have the same affinity and potency as the soluble CD4 alone. See page 7 of the declaration. Dr. Lesslauer thus concludes that the superior results for the TNFR/IgG fusions are unexpected. See page 9 (paragraph 4) of the declaration.

Lesslauer Declaration [III] provides experimental evidence demonstrating unexpectedly superior activity of a recombinant fusion protein comprising the extracellular

domain of the 75 kD TNF receptor (also known as TNFR-II) fused to the hinge region of IgG3 (denoted as "p75sTNFR/IgG" in the Declaration), compared to the soluble TNFR fragment alone. See paragraph 4 of the Declaration. As the spatial geometry of the TNF receptor binding site was not known, it was possible that p75sTNFR/IgG would not even exhibit TNF binding activity (see page 2, Exhibit B.) Dr. Lesslauer states: "Surprisingly, however, the fusion construct obtained even had an excellent binding activity. In addition, an unexpectedly higher kinetic stability and a surprisingly improved inhibition of the effect of TNFα in biological cell culture tests were discovered as well." (Page 2 of Exhibit B of the Declaration.)

Experiment I of Lesslauer Declaration [III] is a binding study that measured dissociation of the test TNF binding protein from radiolabeled TNFα in the presence of unlabeled TNFα. Dissociation of p75sTNFR/IgG fusion was compared to dissociation of p75sTNFR fragment. As shown in the figure, at the six-minute time point, essentially all of the TNFα had dissociated from p75sTNFR, while only about half of the TNFα had dissociated from p75sTNFR/IgG, which indicates p75sTNFR/IgG has a higher kinetic stability than sTNFR.

Experiment II of Lesslauer Declaration [III] investigates the effect of p75sTNFR/IgG on TNF-induced proliferation of mononuclear cells as measured by incorporation of radiolabeled thymidine. As demonstrated in the table, p75sTNFR/IgG inhibited 86% of TNF-induced proliferation while p75sTNFR inhibited 68% of TNF-induced proliferation. This data demonstrated that p75sTNFR/IgG was more effective in neutralizing TNF biological activity. Note that because equal weight amounts of p75sTNFR and p75sTNFR/IgG (which is about twice as heavy as p75sTNFR) were added to the cell culture, on a molar basis only about half as much p75TNFR/IgG was used in Experiment II. Thus, half as much of the IgG3 fusion protein provided a significantly greater neutralization of TNF biological activity.

Further, published data in Mohler *et al.* provides experimental evidence demonstrating unexpectedly superior activity of a recombinant fusion protein comprising the extracellular domain of the 75 kD TNF receptor (also known as TNFR-II) fused to the hinge region of IgG1 (denoted as "sTNFR:Fc" in the article), compared to the soluble TNFR fragment alone. In the studies described in Mohler *et al.*, the extracellular portion of p80

TNFR (also known as TNFR-II) was fused to the Fc portion of human IgG1 (see page 1554, col. 2 bottom) lacking the CH1 domain (see Fig. 1 at page 1550) to make an immunoglobulin fusion protein called sTNFR:Fc. As depicted in Figure 2 of Mohler *et al.*, the sTNFR:Fc had about 50 fold higher binding affinity for TNF than the sTNFR (page 1550, col. 2 and Fig. 2A). In addition, the sTNFR:Fc was about 1000 fold more effective in neutralizing TNF-induced cytotoxicity in L929 cells (page 1551, col. 1 and Fig. 2B). Therefore, in addition to the unexpectedly increased binding affinity of the fusion protein as compared to the extracellular domain alone (an approximately fifty fold increase), the sTNFR:Fc fusion protein also displayed increased biological activity in an *in vitro*, cell-based assay that was unexpected in magnitude (about 1000 fold) on the basis of the already unexpectedly increased binding affinity.

CONCLUSION

Applicants believe all pending claims are in condition for allowance. If further discussion or amendments would expedite allowance of the claims, the Examiner is asked to contact the undersigned at the number below.

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Respectfully submitted,

By _____

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